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ORIGINAL ARTICLE

MicroRNA-143 and -145 modulate the phenotype of synovial fibroblasts in rheumatoid arthritis

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Fibroblast-like synoviocytes (FLSs) constitute a major cell subset of rheumatoid arthritis (RA) synovia. Dysregulation of microRNAs (miRNAs) has been implicated in activation and proliferation of RA-FLSs. However, the functional association of various miRNAs with their targets that are characteristic of the RA-FLS phenotype has not been globally elucidated. In this study, we performed microarray analyses of miRNAs and mRNAs in RA-FLSs and osteoarthritis FLSs (OA-FLSs), simultaneously, to validate how dysregulated miRNAs may be associated with the RA-FLS phenotype. Global miRNA profiling revealed that miR-143 and miR-145 were differentially upregulated in RA-FLSs compared to OA-FLSs. miR-143 and miR-145 were highly expressed in independent RA-FLSs. The miRNA-target prediction and network model of the predicted targets identified insulin-like growth factor binding protein 5 (IGFBP5) and semaphorin 3A (SEMA3A) as potential target genes downregulated by miR-143 and miR-145, respectively. IGFBP5 level was inversely correlated with miR-143 expression, and its deficiency rendered RA-FLSs more sensitive to TNFα stimulation, promoting IL-6 production and NF-κB activity. Moreover, SEMA3A was a direct target of miR-145, as determined by a luciferase reporter assay, antagonizing $VEGF_{165}$-induced increases in the survival, migration and invasion of RA-FLSs. Taken together, our data suggest that enhanced expression of miR-143 and miR-145 renders RA-FLSs susceptible to TNFα and $VEGF_{165}$ stimuli by downregulating IGFBP5 and SEMA3A, respectively, and that these miRNAs could be therapeutic targets.
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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease that is characterized by chronic inflammatory cell infiltration and pannus formation in synovial tissues that lead to the destruction of articular cartilage and bone. In RA joints, various inflammatory cells become activated via a variety of cytokines and chemokines as well as via cell–cell contact.[1] Among various cell types, fibroblast-like synoviocytes (FLSs) are the most abundant resident cells in the synovial membrane and play critical roles in the pathogenesis of RA. FLSs in an RA patient (RA-FLSs) have tumor-like features, including an increased proliferation rate, anti-apoptotic ability and pro-migratory and pro-invasive properties that cause pannus formation and joint destruction.[2,3] Moreover, RA-FLSs produce large amounts of pro-inflammatory cytokines, including interleukin-1β (IL-1β), IL-6 and tumor necrosis factor α (TNFα), that contribute to the perpetuation of chronic inflammation.[2]

MicroRNAs (miRNAs) have emerged as key regulators of a broad spectrum of cellular functions, such as proliferation, differentiation and apoptosis, that are associated with the pathogenesis of various autoimmune diseases.[4] Evidence is emerging that miRNA expression is dysregulated in RA-FLSs, which may be responsible for various pathologic processes involving RA.[5–8] For example, miR-126 has been identified as a regulator of phosphatidylinositol 3-kinase (PI3K)/AKT in RA-FLSs, an important signaling molecule mediating cell proliferation and apoptosis.[5] In addition, miR-20a has been found to have two target genes in FLSs: thioredoxin interacting protein (TXNIP) and apoptosis signal-regulating kinase (ASK1).[6,7] These mediate NLRP3-inflammasome and TLR4-dependent cytokine release by FLSs, respectively.[6,7] miR-221 has also been identified as a regulator for increased migration and invasion of RA-FLSs.[8] Nevertheless, global and integrated analyses of miRNA and mRNA expression levels, which can

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